

CLAIM AMENDMENTS

1. (Original) A conjugate comprising a ligand, a linker, and a cytotoxic agent, in which the linker is FALA (SEQ ID NO: 1).
2. (Original) The conjugate of claim 1, wherein the ligand is a peptide or a peptidomimetic.
3. (Original) The conjugate of claim 2, wherein the peptidomimetic is a peptoid.
4. (Currently Amended) The conjugate of ~~any of claims~~ claim 1-3, wherein the ligand specifically binds to a receptor selected from the group consisting of:
 - the gastrin (cholecystokinin B (CCKB)) receptor,
 - the cholecystokinin A (CCKA) receptor,
 - the somatostatin receptor,
 - the gastrin-releasing peptide (GRP) receptor,
 - the substance P (neurokinin 1 (NK1)) receptor,
 - the guanylin receptor, and
 - the vasoactive intestinal peptide 1 (VIP-1) receptor.
5. (Original) The conjugate of claim 4, wherein the ligand is selected from the group consisting of:
 - LGPQGPPHLVADPSKKQGPWLEEEEEAYGWMDF (gastrin-34) (SEQ ID NO: 5),
 - an N-terminal truncated derivative of gastrin-34, and
 - W(Nle)DF (SEQ ID NO: 6).
6. (Original) The conjugate of claim 4, wherein the ligand is selected from the group consisting of:
 - D(SfY)MGWMDF (SEQ ID NO: 7),
 - D(SfY)(Nle)GW(Nle)DF (SEQ ID NO: 8), and
 - EEEAYGW(Nle)DF (SEQ ID NO:20).
7. (Original) The conjugate of claim 4, wherein the ligand is selected from the group consisting of:
 - VLPAGGGTVLTKMYPRGNHWAVGHLM (SEQ ID NO: 9),

an N-terminal truncated derivative of VLPAGGGTVLTKMYPRGNHWAVGHLM (SEQ ID NO: 9), and
WAVGHLM (SEQ ID NO: 10).

8. (Original) The conjugate of claim 4, wherein the ligand is selected from the group consisting of:

AGCKNFFWKFTSC (SEQ ID NO: 11), in which the two C residues are disulfide bonded, and
FCFWKTCT(OH) (SEQ ID NO: 12), in which the two C residues are disulfide bonded.

9. (Original) The conjugate of claim 4, wherein the ligand is selected from the group consisting of:

RPLPQQFFGLM (SEQ ID NO: 13) and
an analog of RPLPQQFFGLM (SEQ ID NO: 13).

10. (Original) The conjugate of claim 4, wherein the ligand is selected from the group consisting of:

PGTCEICAYAACTGC (SEQ ID NO: 14), in which the first and third C residues are disulfide bonded, and
PGTCEICAYAACTGC (SEQ ID NO: 14), in which the second and fourth C residues are disulfide bonded.

11. (Original) The conjugate of claim 4, wherein the ligand is selected from the group consisting of:

NDDCELCVACTGCL (SEQ ID NO: 15), in which the first and third C residues are disulfide bonded, and
NDDCELCVACTGCL (SEQ ID NO: 15), in which the second and fourth C residues are disulfide bonded.

12. (Original) The conjugate of claim 4, wherein the ligand is selected from the group consisting of:

NYCCELCCNPACTGCF (SEQ ID NO: 16), in which the first and fourth C residues are disulfide bonded,

NYCCELCCNPACTGCF (SEQ ID NO: 16), in which the second and fifth C residues are disulfide bonded, and

NYCCELCCNPACTGCF (SEQ ID NO: 16), in which the third and sixth C residues are disulfide bonded.

13. (Original) The conjugate of claim 4, wherein the ligand is selected from the group consisting of:

HSDALFTDNYTRLRLQMAVKKYLSILNG (SEQ ID NO: 17) and

HSDALFTDNYTRLRLQ(Nle)AVKKYLSILNG (SEQ ID NO: 18).

14. (Currently Amended) The conjugate of ~~any of claims~~ claim 1-13, wherein the cytotoxic agent is selected from the group consisting of:

cemadotin,

a derivative of cemadotin,

a derivative of hemiasterlin,

esperamicin C,

neocarzinostatin,

maytansinoid DM1,

7-chloromethyl-10,11 methylenedioxy-camptothecin,

rhizoxin, and

the halichondrin B analog, ER-086526.

15. (Original) A conjugate comprising a ligand, a linker, and a cytotoxic agent, in which the linker is VLALA (SEQ ID NO: 2).

16. (Original) The conjugate of claim 15, wherein the ligand is a peptide or a peptidomimetic.

17. (Original) The conjugate of claim 16, wherein the peptidomimetic is a peptoid.

18. (Currently Amended) The conjugate of ~~any of claims~~ claim 15-17, wherein the ligand specifically binds to a receptor selected from the group consisting of:

the gastrin (CCKB) receptor,

the CCKA receptor,

the somatostatin receptor,

the GRP receptor,
the substance P (NK1) receptor,
the guanylin receptor, and
the VIP-1 receptor.

19. (Original) The conjugate of claim 18, wherein the ligand is selected from the group consisting of:
LGPQGPPHLVADPSKKQGPWLEEEEA YGW MDF (gastrin-34) (SEQ ID NO: 5),
an N-terminal truncated derivative of gastrin-34, and
W(Nle)DF (SEQ ID NO: 6).
20. (Original) The conjugate of claim 18, wherein the ligand is selected from the group consisting of:
D(SfY)MGW MDF (SEQ ID NO: 7),
D(SfY)(Nle)GW(Nle)DF (SEQ ID NO: 8), and
EEEAYGW(Nle)DF (SEQ ID NO: 20).
21. (Original) The conjugate of claim 18, wherein the ligand is selected from the group consisting of:
VPLPAGGGTVLTKMYPRGNHWAVGHLM (SEQ ID NO: 9),
an N-terminal truncated derivative of VPLPAGGGTVLTKMYPRGNHWAVGHLM
(SEQ ID NO: 9), and
WAVGHLM (SEQ ID NO: 10).
22. (Original) The conjugate of claim 18, wherein the ligand is selected from the group consisting of:
AGCKNFFWKTFTSC (SEQ ID NO: 11), in which the two C residues are disulfide
bonded, and
FCFWKTCT(OH) (SEQ ID NO: 12), in which the two C residues are disulfide
bonded.
23. (Original) The conjugate of claim 18, wherein the ligand is selected from the group consisting of:
RPLPQQFFGLM (SEQ ID NO: 13) and
an analog of RPLPQQFFGLM (SEQ ID NO: 13).

24. (Original) The conjugate of claim 18, wherein the ligand is selected from the group consisting of:
PGTCEICAYAACTGC (SEQ ID NO: 14), in which the first and third C residues are disulfide bonded, and
PGTCEICAYAACTGC (SEQ ID NO: 14), in which the second and fourth C residues are disulfide bonded.
25. (Original) The conjugate of claim 18, wherein the ligand is selected from the group consisting of:
NDDCELCVACTGCL (SEQ ID NO: 15), in which the first and third C residues are disulfide bonded, and
NDDCELCVACTGCL (SEQ ID NO: 15), in which the second and fourth C residues are disulfide bonded.
26. (Original) The conjugate of claim 18, wherein the ligand is selected from the group consisting of:
NYCCELCCNPACTGCF (SEQ ID NO: 16), in which the first and fourth C residues are disulfide bonded,
NYCCELCCNPACTGCF (SEQ ID NO: 16), in which the second and fifth C residues are disulfide bonded, and
NYCCELCCNPACTGCF (SEQ ID NO: 16), in which the third and sixth C residues are disulfide bonded.
27. (Original) The conjugate of claim 18, wherein the ligand is selected from the group consisting of:
HSDALFTDNYTRLRLQMAVKKYLNSILNG (SEQ ID NO: 17) and
HSDALFTDNYTRLRLQ(Nle)AVKKYLNSILNG (SEQ ID NO: 18).
28. (Currently Amended) The conjugate of ~~any of claims~~ claim 15-27, wherein the cytotoxic agent is selected from the group consisting of:
cemadotin,
a derivative of cemadotin,
a derivative of hemiasterlin,
esperamicin C,

neocarzinostatin,
maytansinoid DM1,
7-chloromethyl-10,11 methylenedioxy-camptothecin,
rhizoxin, and
the halichondrin B analog, ER-086526.

29. – 48. (Cancelled.)

49. (Original) A conjugate comprising a ligand, a linker, and a cytotoxic agent, in which the linker is ChaLALA (SEQ ID NO: 21), ChaChaLAL (SEQ ID NO: 22), NalChaLAL (SEQ ID NO: 23) or NalLALA (SEQ ID NO: 24).

50. (Original) The conjugate of claim 49, wherein the ligand is a peptide or a peptidomimetic.

51. (Original) The conjugate of claim 50, wherein the peptidomimetic is a peptoid.

52. (Currently Amended) The conjugate of ~~any of claims~~ claim 49–51, wherein the ligand specifically binds to a receptor selected from the group consisting of:

the gastrin (cholecystokinin B (CCKB)) receptor,
the cholecystokinin A (CCKA) receptor,
the somatostatin receptor,
the gastrin-releasing peptide (GRP) receptor,
the substance P (neurokinin 1 (NK1)) receptor,
the guanylin receptor, and
the vasoactive intestinal peptide 1 (VIP-1) receptor.

53. (Original) The conjugate of claim 52, wherein the ligand is selected from the group consisting of:

LGPQGPPHLVADPSKKQGPWLEEEEEAYGWMDF (gastrin-34) (SEQ ID NO: 5),
an N-terminal truncated derivative of gastrin-34, and
W(Nle)DF (SEQ ID NO: 6).

54. (Original) The conjugate of claim 52, wherein the ligand is selected from the group consisting of:

D(SfY)MGWMDf (SEQ ID NO: 7),
D(SfY)(Nle)GW(Nle)DF (SEQ ID NO: 8), and
EEEAYGW(Nle)DF (SEQ ID NO:20).

55. (Original) The conjugate of claim 52, wherein the ligand is selected from the group consisting of:

VLPAGGGTVLTKMYPRGNHWAVGHLM (SEQ ID NO: 9),
an N-terminal truncated derivative of VLPAGGGTVLTKMYPRGNHWAVGHLM
(SEQ ID NO: 9), and
WAVGHLM (SEQ ID NO: 10).

56. (Original) The conjugate of claim 52, wherein the ligand is selected from the group consisting of:

AGCKNFFWKTFTSC (SEQ ID NO: 11), in which the two C residues are disulfide
bonded, and
FCFWKTCT(OH) (SEQ ID NO: 12), in which the two C residues are disulfide
bonded.

57. (Original) The conjugate of claim 52, wherein the ligand is selected from the group consisting of:

RPLPQQFFGLM (SEQ ID NO: 13) and
an analog of RPLPQQFFGLM (SEQ ID NO: 13).

58. (Original) The conjugate of claim 52, wherein the ligand is selected from the group consisting of:

PGTCEICAYAACTGC (SEQ ID NO: 14), in which the first and third C residues are
disulfide bonded, and
PGTCEICAYAACTGC (SEQ ID NO: 14), in which the second and fourth C residues
are disulfide bonded.

59. (Original) The conjugate of claim 52, wherein the ligand is selected from the group consisting of:

NDDCELCVACTGCL (SEQ ID NO: 15), in which the first and third C residues are
disulfide bonded, and

NDDCELCVACTGCL (SEQ ID NO: 15), in which the second and fourth C residues are disulfide bonded.

60. (Original) The conjugate of claim 52, wherein the ligand is selected from the group consisting of:

NYCCELCNPACTGCF (SEQ ID NO: 16), in which the first and fourth C residues are disulfide bonded,

NYCCELCNPACTGCF (SEQ ID NO: 16), in which the second and fifth C residues are disulfide bonded, and

NYCCELCNPACTGCF (SEQ ID NO: 16), in which the third and sixth C residues are disulfide bonded.

61. (Original) The conjugate of claim 52, wherein the ligand is selected from the group consisting of:

HSDALFTDNYTRLRLQMAVKKYLSILNG (SEQ ID NO: 17) and

HSDALFTDNYTRLRLQ(Nle)AVKKYLSILNG (SEQ ID NO: 18).

62. (Currently Amended) The conjugate of ~~any of claims~~ claim 49-61, wherein the cytotoxic agent is selected from the group consisting of:

cemadotin,

a derivative of cemadotin,

a derivative of hemiasterlin,

esperamicin C,

neocarzinostatin,

maytansinoid DM1,

7-chloromethyl-10,11 methylenedioxy-camptothecin,

rhizoxin, and

the halichondrin B analog, ER-086526.

63. (Currently Amended) A composition comprising the conjugate of ~~any of claims~~ claim 1-14 and a carrier.

64. (Currently Amended) A composition comprising the conjugate of ~~any of claims~~ claim 15-28 and a carrier.

65. (Cancelled).

66. (Cancelled).

67. (Currently Amended) A composition comprising the conjugate of ~~any of claims~~ claim 49-62 and a carrier

68. (Currently Amended) A method of delivering a cytotoxic agent in a cell-specific manner, which method comprises administering the conjugate of ~~any of claims~~ claim 1-14 to a collection of cells comprising a receptor to which the ligand of the conjugate binds, whereupon the cytotoxic agent is administered to the cells in a cell-specific manner.

69. (Original) The method of claim 68, wherein the cells are in vivo.

70. (Currently Amended) A method of delivering a cytotoxic agent in a cell-specific manner, which method comprises administering the conjugate of ~~any of claims~~ claim 15-28 to a collection of cells comprising a receptor to which the ligand of the conjugate binds, whereupon the cytotoxic agent is administered to the cells in a cell-specific manner.

71. (Original) The method of claim 70, wherein the cells are in vivo.

72. – 75. (Cancelled).

76. (Currently Amended) A method of delivering a cytotoxic agent in a cell-specific manner, which method comprises administering the conjugate of ~~any of claims~~ claim 49-62 to a collection of cells comprising a receptor to which the ligand of the conjugate binds, whereupon the cytotoxic agent is administered to the cells in a cell-specific manner.

77. (Original) The method of claim 76, wherein the cells are in vivo.

78. (Currently Amended) A method of treating cancer in a mammal, which method comprises administering a cancer-treating effective amount of the conjugate of ~~any of claims~~ claim 1-14 to the mammal, whereupon the mammal is treated for cancer.

79. (Original) The method of claim 78, wherein the cancer is cancer of the lung, stomach, colon, breast, or pancreas.

80. (Currently Amended) A method of treating cancer in a mammal, which method comprises administering a cancer-treating effective amount of the conjugate of ~~any of claims~~ claim 15-28 to the mammal, whereupon the mammal is treated for cancer.

81. (Original) The method of claim 80, wherein the cancer is cancer of the lung, stomach, colon, breast, or pancreas.

82. – 85. (Cancelled).

86. (Currently Amended) A method of treating cancer in a mammal, which method comprises administering a cancer-treating effective amount of the conjugate of ~~any of claims~~ claim 49-62 to the mammal, whereupon the mammal is treated for cancer.

87. (Original) The method of claim 86, wherein the cancer is cancer of the lung, stomach, colon, breast, or pancreas.

88. (New) A conjugate comprising a ligand, a linker and a cytotoxic agents, in which the linker is ALAL (SEQ ID NO: 3) and the ligand specifically binds to a receptor selected from the group consisting of:

- the gastrin (cholecystokinin B (CCKB)) receptor,
- the cholecystokinin A (CCKA) receptor,
- the somatostatin receptor,
- the gastrin-releasing peptide (GRP) receptor,
- the substance P (neurokinin 1 (NK1)) receptor,
- the guanylin receptor, and
- the vasoactive intestinal peptide 1 (VIP-1) receptor.

89. (New) The conjugate of claim 88, wherein the ligand is selected from the group consisting of:

- LGPQGPPHLVADPSKKQGPWLEEEEEAYGWMDF (gastrin-34) (SEQ ID NO: 5),
- an N-terminal truncated derivative of gastrin-34, and
- W(Nle)DF (SEQ ID NO: 6).

90. (New) The conjugate of claim 88, wherein the ligand is selected from the group consisting of:

D(SfY)MGWMDf (SEQ ID NO: 7),
D(SfY)(Nle)GW(Nle)DF (SEQ ID NO: 8), and
EEEAYGW(Nle)DF (SEQ ID NO: 20).

91. (New) The conjugate of claim 88, wherein the ligand is selected from the group consisting of:

VLPAGGGTVLTKMYPRGNHWAVGHLM (SEQ ID NO: 9),
an N-terminal truncated derivative of VLPAGGGTVLTKMYPRGNHWAVGHLM
(SEQ ID NO: 9), and
WAVGHLM (SEQ ID NO: 10).

92. (New) The conjugate of claim 88, wherein the ligand is selected from the group consisting of:

AGCKNFFWKFTSC (SEQ ID NO: 11), in which the two C residues are disulfide
bonded, and
FCFWKTCT(OH) (SEQ ID NO: 12), in which the two C residues are disulfide
bonded.

93. (New) The conjugate of claim 88, wherein the ligand is selected from the group consisting of:

RPLPQQFFGLM (SEQ ID NO: 13) and
an analog of RPLPQQFFGLM (SEQ ID NO: 13).

94. (New) The conjugate of claim 88, wherein the ligand is selected from the group consisting of:

PGTCEICAYAACTGC (SEQ ID NO: 14), in which the first and third C residues are
disulfide bonded, and
PGTCEICAYAACTGC (SEQ ID NO: 14), in which the second and fourth C residues
are disulfide bonded.

95. (New) The conjugate of claim 88, wherein the ligand is selected from the group consisting of:

NDDCELCVACTGCL (SEQ ID NO: 15), in which the first and third C residues are disulfide bonded, and

NDDCELCVACTGCL (SEQ ID NO: 15), in which the second and fourth C residues are disulfide bonded.

96. (New) The conjugate of claim 88, wherein the ligand is selected from the group consisting of:

NYCCELCNPACTGCF (SEQ ID NO: 16), in which the first and fourth C residues are disulfide bonded,

NYCCELCNPACTGCF (SEQ ID NO: 16), in which the second and fifth C residues are disulfide bonded, and

NYCCELCNPACTGCF (SEQ ID NO: 16), in which the third and sixth C residues are disulfide bonded. -

97. (New) The conjugate of claim 88, wherein the ligand is selected from the group consisting of:

HSDALFTDNYTRLRLQMAVKKYLSILNG (SEQ ID NO: 17) and

HSDALFTDNYTRLRLQ(Nle)AVKKYLSILNG (SEQ ID NO: 18).

98. (New) The conjugate of claim 88, wherein the cytotoxic agent, is selected from the group consisting of:

cemadotin,

a derivative of cemadotin,

a derivative of hemiasterlin,

esperamicin C,

neocarzinostatin,

maytansinoid DM1,

7-chloromethyl-10,11 methylenedioxy-camptothecin,

rhizoxin, and

the halichondrin B analog, ER-086526.

99. (New) A conjugate comprising a ligand, a linker, and a cytotoxic agent, in which the linker is ALALA (SEQ ID NO: 4), wherein the ligand specifically binds to a receptor selected from the group consisting of:

the gastrin (cholecystokinin B (CCKB)) receptor,

the cholecystokinin A (CCKA) receptor,
the somatostatin receptor,
the gastrin-releasing peptide (GRP) receptor,
the substance P (neurokinin 1 (NK1)) receptor,
the guanylin receptor, and
the vasoactive intestinal peptide 1 (VIP-1) receptor.

100. (New) The conjugate of claim 99, wherein the ligand is selected from the group consisting of:

LGPQGPPHLVADPSKKQGPWLEEEEEAYGWMDf (gastrin-34) (SEQ ID NO: 5),
an N-terminal truncated derivative of gastrin-34, provided that the derivative is not
AYGW(Nle)DF (SEQ ID NO: 19), and
W(Nle)DF (SEQ ID NO: 6).

101. (New) The conjugate of claim 99, wherein the ligand is selected from the group consisting of:

D(SfY)MGWMDf (SEQ ID NO: 7),
D(SfY)(Nle)GW(Nle)DF (SEQ ID NO: 8), and
EEEAYGW(Nle)DF (SEQ ID NO: 20).

102. (New) The conjugate of claim 99, wherein the ligand is selected from the group consisting of:

VLPAGGGTVLTKMYPRGNHWAVGHLM (SEQ ID NO: 9),
an N-terminal truncated derivative of VLPAGGGTVLTKMYPRGNHWAVGHLM
(SEQ ID NO: 9), and
WAVGHLM (SEQ ID NO: 10).

103. (New) The conjugate of claim 99, wherein the ligand is selected from the group consisting of:

AGCKNFFWKTFTSC (SEQ ID NO: 11), in which the two C residues are disulfide
bonded, and
FCFWKTCT(OH) (SEQ ID NO: 12), in which the two C residues are disulfide
bonded.

104. (New) The conjugate of claim 99, wherein the ligand is selected from the group consisting of:

RPLPQQFFGLM (SEQ ID NO: 13) and
an analog of RPLPQQFFGLM (SEQ ID NO: 13).

105. (New) The conjugate of claim 99, wherein the ligand is selected from the group consisting of:

PGTCEICAYAACTGC (SEQ ID NO: 14), in which the first and third C residues are disulfide bonded, and
PGTCEICAYAACTGC (SEQ ID NO: 14), in which the second and fourth C residues are disulfide bonded.

106. (New) The conjugate of claim 99, wherein the ligand is selected from the group consisting of:

NDDCELCVACTGCL (SEQ ID NO: 15), in which the first and third C residues are disulfide bonded, and
NDDCELCVACTGCL (SEQ ID NO: 15), in which the second and fourth C residues are disulfide bonded.

107. (New) The conjugate of claim 99, wherein the ligand is selected from the group consisting of:

NYCCELCCNPACTGCF (SEQ ID NO: 16), in which the first and fourth C residues are disulfide bonded,
NYCCELCCNPACTGCF (SEQ ID NO: 16), in which the second and fifth C residues are disulfide bonded, and
NYCCELCCNPACTGCF (SEQ ID NO: 16), in which the third and sixth C residues are disulfide bonded.

108. (New) The conjugate of claim 99, wherein the ligand is selected from the group consisting of:

HSDALFTDNYTRLRLQMAVKKYLSILNG (SEQ ID NO: 17) and
HSDALFTDNYTRLRLQ(Nle)AVKKYLSILNG (SEQ ID NO: 18).

109. (New) The conjugate of claim 99, wherein the cytotoxic agent is selected from the group consisting of:

cemadotin,
a derivative of cemadotin,
a derivative of hemiasterlin,
esperamicin C,
neocarzinostatin,
maytansinoid DM1,
7-chloromethyl-10,11 methylenedioxy-camptothecin,
rhizoxin, and
the halichondrin B analog, ER-086526.

110. (New) A composition comprising the conjugate of claim 88 and a carrier.
111. (New) A composition comprising the conjugate of claim 99 and a carrier.
112. (New) A method of delivering a cytotoxic agent in a cell-specific manner, which method comprises administering the conjugate of claim 88 to a collection of cells comprising a receptor to which the ligand of the conjugate binds, whereupon the cytotoxic agent is administered to the cells in a cell-specific manner.
113. (New) The method of claim 112, wherein the cells are in vivo.
114. (New) A method of delivering a cytotoxic agent in a cell-specific manner, which method comprises administering the conjugate of claim 99 to a collection of cells comprising a receptor to which the ligand of the conjugate binds, whereupon the cytotoxic agent is administered to the cells in a cell-specific manner.
115. (New) The method of claim 114, wherein the cells are in vivo.
116. (New) A method of treating cancer in a mammal, which method comprises administering a cancer-treating effective amount of the conjugate of claim 88 to the mammal, whereupon the mammal is treated for cancer.
117. (New) The method of claim 116, wherein the cancer is cancer of the lung, stomach, colon, breast, or pancreas.

118. (New) A method of treating cancer in a mammal, which method comprises administering a cancer-treating effective amount of the conjugate of claim 99 to the mammal, whereupon the mammal is treated for cancer.

119. The method of claim 118, wherein the cancer is cancer of the lung, stomach, colon, breast, or pancreas.